PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of DREAM3R- DuRvalumab with chEmotherapy as first line treAtment in advanced pleural Mesothelioma - A phase 3 Randomised trial
AUTHORS	Kok, Peey Sei; Forde, Patrick M; Hughes, Brett; Sun, Zhuoxin; Brown, Chris; Ramalingam, Suresh; Cook, Alistair; Lesterhuis, Willem Joost; Yip, Sonia; O'Byrne, Ken; Pavlakis, Nick; Brahmer, Julie; Anagnostou, Valsamo; Ford, Kate; Fitzpatrick, Karen; Bricker, Alison; Cummins, Michelle M; Stockler, Martin; Nowak, Anna

VERSION 1 – REVIEW

REVIEWER	Steven Gray Trinity College Dublin, Clinical Medicine
REVIEW RETURNED	12-Oct-2021

GENERAL COMMENTS	Overall, this is a standard Trial Study Protocol. There are no major issues/concerns. I do have two minor issues that can probably be dealt with very quickly a) Will equal numbers of ECOG 1 and ECOG 0 status patients be recruited? b) As AstraZeneca is the funder should it not also be classed as the Sponsor as well?

REVIEWER	A K Guntulu Eskisehir Osmangazi University, Department of Chest Disease
REVIEW RETURNED	22-Oct-2021

GENERAL COMMENTS	I congratulate the researchers for planning such a study. This is a well-designed randomized trial evaluating durvalumab on mesothelioma. Also, using stratification factors is one of the interesting parts of the study. I'm wondering about the results of this study.

REVIEWER	Bushra Mina Lenox Hill Hospital, Pulmonary critical care medicine
REVIEW RETURNED	15-Nov-2021

GENERAL COMMENTS	- need to expand on the limitation of the study - The study is well written. The Primary, secondary and tertiary outcomes outlined well and covers all aspects-patient outcomes and QOL, safety, cost, and biomarkers including imaging. - Inclusion and exclusion criteria appropriate - Author listed previous studies immunotherapies, Bevacizumab-nintedanib- pembrolizumab, and dual therapy with nivolumab plus ipilimumab. Author did not explain the benefit of Durvalumab in comparison to the other agents and it's mode of action. He did not

	list the side effects in details as part of the protocol

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Steven Gray, Trinity College Dublin, St James's Hospital

Comments to the Author:
Overall, this is a standard Trial Study Protocol.
There are no major issues/concerns.
I do have two minor issues that can probably be dealt with very quickly

a) Will equal numbers of ECOG 1 and ECOG 0 status patients be recruited?
Authors: It is unlikely that there will be equal numbers of ECOG 0 and ECOG 1 recruited.

b) As AstraZeneca is the funder should it not also be classed as the Sponsor as well?
Authors: This is an academically-sponsored, investigator-initiated study. University of Sydney is the global and ANZ sponsor, PrECOG is the sponsor for the USA. The investigator team is responsible for all aspects of the trial, including scientific oversight, study coordination, data acquisition and management, statistical analysis and reporting.
MedImmune Ltd is providing the funding and AstraZeneca is providing study drug. This is now updated in pg 21 the revised manuscript.

Reviewer: 2
Prof. A K Guntulu, Eskisehir Osmangazi University

Comments to the Author:
I congratulate the researchers for planning such a study. This is a well-designed randomized trial evaluating durvalumab on mesothelioma. Also, using stratification factors is one of the interesting parts of the study. I'm wondering about the results of this study.
Authors: We thank the reviewer for the kind comments. We commenced recruitment in February 2021. The target accrual time is 27 months with an additional 24 months follow up time (by May 2023) and release the results after this.

Reviewer: 3
Dr. Bushra Mina, Lenox Hill Hospital

Comments to the Author:
- need to expand on the limitation of the study
Authors: We have now removed the last bullet point and revised it to the following (bold), as a limitation of the study

- International, open-labelled, randomised phase 3 trial of immunotherapy and chemotherapy in first line treatment of pleural mesothelioma
- Strong biological rationale and earlier phase clinical data
- Extensive translational science biospecimen collection and plans
- **This study does not contain a comparator arm of ipilimumab-nivolumab combination, which is a new option for first line treatment, particularly for sarcomatoid disease**
- **The control arm (Cisplatin/Carboplatin plus pemetrexed) does not include bevacizumab, which is an option for first line treatment.**

- The study is well written. The Primary, secondary and tertiary outcomes outlined well and covers all aspects-patient outcomes and QOL, safety, cost, and biomarkers including imaging.
- Inclusion and exclusion criteria appropriate

- Author listed previous studies immunotherapies, Bevacizumab- nintedanib- pembrolizumab, and dual therapy with nivolumab plus ipilimumab. Author did not explain the benefit of Durvalumab in comparison to the other agents and it's mode of action. He did not list the side effects in details as part of the protocol

Authors: We have added further information to specify the mode of action and side effects of durvalumab in pg 6 and 7. **"**Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1. The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD1 and CD80 (B7.1). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell dependent mechanism.[1] Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response.

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis including pemphigoid, myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g., Guillain-Barré syndrome, myasthenia gravis)."

There is no study that directly compares Durvalumab vs other agents in mesothelioma. However, as we have outlined under the Rationale of the study (pg 5-6), two single-arm first line phase 2 trials (DREAM and PrECOG 0505) combining durvalumab with platinum-based doublet chemotherapy showed encouraging activity and acceptable safety, hence the importance of this study.